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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,161	10/15/2003	R. Terry Dunlay	97,022-B2-CO	6805
20306 7590 09/20/2007 MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP 300 S. WACKER DRIVE 32ND FLOOR CHICAGO, IL 60606			EXAMINER WHALEY, PABLO S	
			ART UNIT 1631	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/686,161

Applicant(s)

DUNLAY ET AL.

Examiner

Pablo Whaley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44-50 and 52-56 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-50 and 52-56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>06/26/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants' remarks, filed 06/26/2007, have been fully considered. The following rejections and/or objections are maintained, newly applied, or withdrawn for the reasons set forth below. They constitute the complete set presently being applied to the instant application.

RESTRICTION REQUIREMENT VACATED

It is noted that the restriction requirement mailed 7/06/2006 was vacated on 8/9/2006 in view of the preliminary amendment filed 10/15/2003.

STATUS OF THE CLAIMS

Claims 44-50 and 52-56 are herein under examination. Claims 1-43 and 51 have been canceled.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statement filed 06/26/2007 has been considered in full.

PRIORITY

Priority to US Provisional Application 09/031,271, filed 2/27/1998 has been acknowledged.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-50 and 52-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is rejected for the following reasons. Claims which are directly or indirectly dependent from claim 44 are also included as rejected herein, due to said dependence.

Claim 44 now recites "wherein the program results are displayed to a user." There is lack antecedent basis for "the program results," as there is no prior recitation of any result. Correction is requested. As a result, it is unclear whether the intended "result" is determining ratios, differences, and/or intensities as in steps b) and c). Clarification is requested via clearer claim language.

CLAIM REJECTIONS - 35 USC § 101

The rejection of claims 44-50 and 52-56 under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter is hereby withdrawn in view of applicant's amendments to the claims.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The rejection of claims 44, 50, 51, 52, 53, 55, and 56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, and 8 of US 6,671,624, issued Dec. 30, 2003 is hereby withdrawn in view of the Terminal Disclaimer, filed 06/27/2007.

CLAIM REJECTIONS - 35 USC §112, 1st Paragraph

The rejection of claims 44-50 and 52-56 under 35 U.S.C. 112, first paragraph, is hereby withdrawn in view of applicant's amendments and arguments.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44-49, 53, and 56 are rejected under 35 U.S.C. 102 (b) as being anticipated by Kamensky et al. (US 5,427,910; Issued Jun. 27, 1995).

Applicant's arguments that Kamentsky et al. do not teach defining "cellular organelle masks" are not persuasive, as this limitation is not recited in claim 44.

Applicant's arguments that the distance parameter between labeled chromosomes is not within the "intact cells" is not persuasive in view of Fig. 6, for example, which shows scanned cells with first and second compartments (i.e. compartment masks) as well as distance parameters between intact cells, one with two fluorescent spots and the second with one fluorescent spot.

Applicant's arguments that Kamentsky et al. do not teach or suggest determining translocation of the labeled cellular components between organelles, or taking a ratio or different of the intensity of the luminescent signals are not persuasive for the following reasons. The Examiner has broadly interpreted the distance parameters taught by Kamentsky et al. as a teaching for the differences in the intensity of luminescent signals, as this metric is based on digitized optical signals obtained from cell samples with detectable probes [See Ref. Claim 14]. Fluorescent spot counts are also correlated with distance calculations and displayed to a user [Fig. 8A-F]. Furthermore, Kamentsky et al. teach cells stained with two different probes, each tagged with a different dye such as CY3 and fluorescein are emitting energy at different wavelengths when excited by one or more lasers, can be scanned to define regions that can be independently located simultaneously for each cell, and the distance between them determined and the distance parameters used to detect cells with translocations between chromosomes [See: Col. 15, lines 15-40]. As set forth in the previous office action, mailed 03/16/2007, Kamentsky also teach the following aspects of dependent claims 45-49, 53, and 56: programs and software (i.e. machine readable storage medium) [Col. 12, 1-20] and computer system comprising memory (i.e. database) [Col. 8, lines 1-20] for implementing the above procedures and storing data in memory; listing of property values for each region [Col. 13, lines 45-50] and

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reading of data files (i.e. summary data) for user review [Col. 16, lines 5-15]; lives cells and performing image scanning at different times [Col. 13, lines 50-60] and [Ref. Claim 22]. It is also noted that while claim 44 has been amended to recite the phrase wherein the first and second cellular compartments are different, this amendment is part of the preamble, and therefore has not been given patentable weight. For these reasons, the Examiner maintains the Kamentsky et al. teach all aspects of the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 44-50, 52, 53, and 56 are rejected under 35 U.S.C. 103(a) as being made obvious by Mason et al. (Fluorescent and Luminescent Probes for Biological Activity, 1993, Chapter 12, p.161-195), in view of Wright et al. (Journal of Experimental Botany, March 1996, Vol. 47, No. 296, pp. 439-445). This rejection is newly applied.

Mason et al. teach a computer system for fluorescent ratio imaging of cells [p.174, Section 12.13]. The system includes software and hardware for storage, analysis, and display of all data, as in claims 44-49. In particular, the system provides a means for spatial digitization of cells (i.e. masking) [See Fig. 12.15 and Plate 29.1 for example], wherein pixel intensity profiling [See Fig. 12.16, Plate 29.1, and 29.2] and ratio analysis [Plate 13.2] are both used to compare spatial and temporal differences in the distribution (i.e. translocation) of fluorescent probes at a plurality of locations between different cellular compartments which include the cytoplasm, cell wall, and nucleus, as in claims 44, 50, 52, 53, and 56.

Mason et al. do not specifically teach the translocation between the nucleus and cytoplasm and the cytoplasm and cell member based on differences between two different probe signals, as in claim 50 and 52. However, Mason et al. clearly teach the use of different types of probes for measuring cellular distribution [See Plate 10.1 additionally]. Therefore, it would be well within the ordinary skill of one in the art to use the differences in optical density measurements of obtained from different probes accumulated in the cell nuclei or cytoplasm [Fig. 9] as a measure of translocation of material between the cell nucleus or cytoplasm, as in claims 50 and 52.

Wright et al. teach the use of confocal microscopy techniques for determining the intercellular distribution (i.e. translocation) of multiple fluorescent probes in plant cells [Abstract], and results wherein the translocation of fluorescent markers was observed in the cytoplasm and nuclei of adjacent cells [p.441, Results] and [Fig. 2A, 2B], which also includes translocation across the cell membrane. Therefore Wright et al. teaches the limitations of claims 50, 52, and 53.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to use the system of Mason et al. for analyzing the intercellular fluorescent markers, taught by Wright et al., as Mason et al. clearly teach the use of confocal microscopy for analysis of cellular specimens [Section 12.9], where the motivation would be have been to improve the determination of cell-to-cell interactions and intercellular pathways in plants [Wright et al., p.444, Col. 1].

Claims 44-50 and 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (WO/1997/045730; Published Dec. 12, 1997), in view of Bastiaens et al. (Proc. Natl. Acad. Sci. USA, August 1996, Vol. 93, pp. 8407-8412) and the legal decision of *In re Venner* [262 F.2d91, 95, 120 USPQ 193, 194 (CCPA 1958)]. This rejection is newly applied.

The instant claims are directed to a machine readable storage medium comprising a program containing procedures comprising: (a) defining a first and second cellular compartment mask in multiple individual cells from luminescent signals obtained from a plurality of luminescent reporter molecules; (b) determining an intensity of the luminescent signals from the "at least second" reporter molecule in the first cellular compartment mask and the second cellular compartment mask; and (c) determining a ratio and/or a difference of the intensity of luminescent signals form the at least second reporter molecule in the first cellular compartment mask and the second cellular compartment mask, wherein the ratio and/or difference provides a measure of translocation of the cellular component of interest.

Taylor teaches a miniaturized cell array methods and apparatus for cell-based screening that combine multicolor luminescence reading, microfluidic delivery, and environmental control of living cells in non-uniform micro-patterned arrays [Abstract and p.12]. In particular, Taylor

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teaches the following aspects of the instantly claimed invention: Determining binary images (i.e. compartment masks) for two fluorescent probe signals obtained from an array of cells [p.28 and Fig. 3A and 3B], as in claim 44. An optical mask, which could also be broadly interpreted as a compartment mask, of a desired array is also used and is placed over the surface of the wells for controlling the position and number of wells which receive light is controlled [p.21, ¶4], as in claim 44. A two level screen for insulin mimetics wherein cells carrying a Blue Fluorescent Protein (first reporter) are arranged on the micro-patterned array of cells arrays, and then loaded with a calcium indicator (second reporter), as in claims 44, 53, and 54. Also disclosed is the means to detect, record, and analyze the luminescent signals and the computer means to receive and process digital signals from light detectors [p.14], as well as a computer system for displaying results [Fig. 12], as in claims 44-49. The array of locations are then simultaneously treated with an array of compounds using the microfluidic delivery system, and a short sequence of Fluo-3 images of the whole non-uniform micro-patterned array of cells are analyzed for wells exhibiting a calcium response in the high throughput mode, as in claims 44-45 and 55. The wells containing compounds that induced a response, are then analyzed on a cell by cell basis for evidence of GLUT4 translocation from the cytoplasm to the plasma membrane using blue fluorescence detected in time and space [See Example 1 and Fig. 18], as in claims 44, 50, 52, and 56.

Taylor does not specifically teach a machine readable storage medium comprising a program, the determination of a "ratio" of the intensity of signals from reporter molecules, or translocation from the cytoplasm to the nucleus, as in claims 44 and 50. However, Taylor provides methods for determining an average response in a single well, and counting the numbers of a particular cell subtype in a well [p.11]. Thus, it would have been well within the

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capabilities of one of ordinary skill in the art to determine differences in intensity signals in the different wells as a measure of translocation of particular components of interest.

Bastiaens et al. teach a system that uses quantitative confocal laser scanning microscopy, fluorescence lifetime imaging microscopy, and novel determinations of fluorescence resonance energy transfer (FRET) for observing the translocation of fluorescent labeled proteins in response to stimulation factors and determining their molecular state in different cellular compartments [p.8407, Col. 1 and Col. 2, ¶1]. In particular, fluorescent protein ratios are calculated [p.8408, Results], and the localization of two different fluorescent labeled proteins in cells is displayed such that differences between the two labels are presented as color-coded fluorescent intensity profiles as a measure of translocation of microinjected proteins from the cytoplasm into the cell nucleus [Fig. 3] and [p.8409, Col. 2], as in claims 44 and 50.

In re Venner is a legal decision which indicates that automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish the prior art in terms of patentability. it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to perform any step of the previously stated methods of Taylor according to *In re Venner*.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the method of Taylor using the microspectroscopic translocation strategy taught by Bastiaens et al., since methods for high spatial and temporal resolution imaging measurements of the distribution, amount and biochemical environments of the fluorescent reporter molecules in the cells is well known in the art [Taylor, p.8 and 9], resulting in the practice of the instantly claimed invention with predictable results. One of ordinary skill in the art would have been motivated to use the microspectroscopic translocation strategy taught by Bastiaens et al. to improve intracellular translocation detection since it has been shown to be

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effective for studying signal transduction in living cells, and does not require absolute cytochemical specificity (for the target protein) of the antibody [p.8412, Col. 1]. Furthermore, as Taylor teaches a high throughput analysis system comprising a computer [Fig. 12], coupled with automated loading and handling, that allows for the screening hundreds of compounds a minute [p.35 and p.36] and presents automated analysis techniques [p.9], it would have been well within the capabilities of one of ordinary skill in the art to develop machine readable storage medium for causing a screening system to execute procedures as in claim 44.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Pablo S. Whaley

Patent Examiner

Art Unit 1631

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MICHAEL BORIN, PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'MBorin', is written over the printed name and title of the primary examiner.